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Risk Assessment of N-Nitroso Compounds for Human Health

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Analysis of Volatile N-Nitrosamines in Mainstream and Sidestream Smoke from Cigarettes by GLC-TEA

Klaus D. Brunnemann, Walter Fink and Fritz Moser

Philip Morris Europe, Research Division, Neuchâtel

Key Words. Nitrosamines · Thermal Energy Analyzer (TEA) · Tobacco · Cigarettes · Chromatography

Abstract. Volatile N-nitrosamines were quantitatively determined in mainstream and sidestream smoke of commercial cigarettes using gas chromatography-thermal energy analysis (GLC-TEA). The smoke was trapped in ascorbic acid solution buffered at pH 4.5 and then extracted with dichloromethane; the organic phase was chromatographed on basic alumina and analyzed by GLC-TEA. The mainstream smoke of 22 different commercial cigarettes from Germany and Switzerland contained between 0.1 and 27 ng dimethylnitrosamine (DMN), 1.5 and 29 ng nitrosopyrrolidine (NPY) and traces of methylethylnitrosamine (MEN). The sidestream smoke of these cigarettes contained between 143 and 415 ng DMN, 3.1 and 27 ng MEN and 28 and 150 ng NPY. In a final experiment we measured the DMN concentration in a sealed experimental chamber as a function of the number of cigarettes smoked and recovered 68–87% of the DMN values found when using the sidestream collection device applied in the other experiments.

Introduction

In recent years a great number of studies on the analysis of N-nitrosamines have been conducted. The presence of volatile nitrosamines in tobacco smoke has been known through many studies [1–14]; nonvolatile N-nitrosamines in tobacco and tobacco smoke have been the subject of many other investigators [15–19]. N-nitrosamines have also been detected in other sources such as foodstuffs [20–22], cutting fluids [23, 24], body fluids [22, 25], cosmetics [26], in outdoor environments [27, 28], in indoor environments [29] and recently in beer [30]. A comparison of the nitrosamine yields is illustrated in table I. It was also calculated that the average daily intake of DMN for male persons in Germany amounts to 1.1 μg, 64% of that which is contributed by beer [31].

Earlier studies required elaborate enrichment procedures for the detection and quantitative analysis of nitrosamines. The development of the highly sensitive and specific thermal energy analyzer by *Fine et al.* [32] significantly simplifies the quantitative determination of nitrosamines. Its mechanism of operation has been described earlier [1, 32].

In order to measure nitrosamines in tobacco smoke, the freshly generated aerosol is trapped in ascorbic acid solution at pH 4.5. The inhibiting effect of ascorbic acid on the artifactual nitrosamine formation has been described in several publications [33–35].

The present study reports *new* quantitative data for volatile nitrosamines in fresh mainstream and sidestream smoke of commercial cigarettes. The amount of DMN in a sealed experimental chamber filled with various concentrations of cigarette smoke was also measured.

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Table 1. Presence of nitrosamines in different sources

Source	Nitrosamine[1]	Amount	Reference
Cheese	DMN	1–6 ppb	*Eisenbrand et al.* [20]
Bacon	NPY	4–139 ppb	*Havery et al.* [21]
Grinding fluid	NDEIA	200–800 ppm	*Zingmark and Rappe* [23]
Cutting fluid	NDEIA	200–30,000 ppm	*Fan et al.* [24]
Blood	DMN	0.1–0.8 ppb	*Fine et al.* [25]
Blood	DEN	0.1–0.5 ppb	*Fine et al.* [25]
Cosmetics	NDEIA	up to 25 ppm	*Fan et al.* [26]
Outdoor air	DMN	0.016–0.76 ng/l	*Fine et al.* [28]
Indoor air	DMN	0.01–0.24 ng/l	*Brunnemann et al.* [29]
Tobacco	NNN	1.9–6.6 ppm	*Hoffmann et al.* [19]
Tobacco	DMN	6.9–188 ppb	*Brunnemann et al.* [1]
Tobacco smoke, mainstream	DMN	1.7–97 ng/cig	*Brunnemann et al.* [1]
Tobacco smoke, sidestream	DMN	680–1,770 ng/cig	*Brunnemann et al.* [1]
Beer	DMN	0.2–68 ppb	*Spiegelhalder et al.* [30]

DMN = Dimethylnitrosamine; NPY = nitrosopyrrolidine; NDEIA = nitrosodiethanolamine; DEN = diethylnitrosamine; NNN = nitrosonornicotine

Materials and Methods

Apparatus

For the generation of the mainstream smoke we used a 20-port automatic smoker (Model RM20/CS, H. Borgwaldt, Hamburg, FRG) and for the sidestream smoke analysis we utilized a single-channel smoker (our own construction) and a sidestream smoke apparatus (R. E. Ewald, Queens, N.Y.) with an airflow rate of 25 ml/sec [36].

For the analysis we used a Hewlett-Packard Model 5710A gas chromatograph interfaced with a Thermal Energy Analyzer (Model TEA-502LC, Thermo Electron Corp., Waltham, Mass.) and a Hewlett-Packard Model 3380A recording integrator; the gas chromatograph was equipped with a Model 7671A automatic sampler. For the sampling in the experimental chamber, we used an MSA Monitaire Sampler Model S (Mine Safety Appliances Co., Pittsburgh, Pa.).

Reagents

DMN was purchased from Aldrich-Europe, Belgium, DEN and NPY were purchased from Fluka AG, Buchs, Switzerland and all other N-nitrosamine standards were synthesized in our own laboratories. DMN-^{14}C (4.8 mCi/mmol) and NPY-^{14}C (16.2 mCi/mmol) were obtained from NEN Chemicals, Dreieich, FRG.

Cigarettes

All commercial cigarettes were purchased on the open market in Germany and Switzerland during 1978. The cigarettes were stored for at least 24 h in a humidity chamber at 22 ± 2 °C at relative humidity of 60 ± 3% and were then selected by weight (± 20 mg of average weight of 200 cigarettes). The tobacco products were smoked in a laboratory maintained at relative humidity of 60 ± 5% at 22 ± 2 °C. Throughout the study we applied the standard smoking conditions of 1 puff/min; puff duration, 2 sec; puff volume, 35 ml; and butt length, 23 mm; for products with filter tips, butt length was determined by the filter plus 8 mm or tipping plus 3 mm, whichever was longer [37].

Mainstream Smoke

60 weight-selected cigarettes were smoked by a 20-port automatic smoker. A rotating head flushing nitrogen into every second port was not used since we did not observe significant differences in the volatile nitrosamine data obtained with a rotating head.

The mainstream smoke was led through 2 gas wash bottles containing 100 ml citrate-phosphate buffer, pH 4.5, with 20 m*M* of ascorbic acid. We did not add DMN-^{14}C as internal standard but carried out separate recovery experiments since the contribution from the DMN-^{14}C on the final TEA signal was rather high; however, we used di-isobutylnitrosamine (retention time 10 min) as our internal standard for gas chromatographic analysis.

The buffer solution was extracted 4 times with 100 ml dichloromethane. The organic phase was concentrated to 5 ml and chromatographed on a column of 65 g basic alumina Woelm (activity II–III) with 300 ml dichloromethane. The eluted fraction was concentrated at 35 °C and then analyzed by GLC-TEA. The gas chromatograms were obtained on a 20 ft × 1/8 inch stainless steel column packed with 10% Carbowax 20M-TPA on Gas Chrom Q (80–100 mesh); oven program: 16 min at 180 °C, 32 °C/min to 210 °C, 16 min at 210 °C; injection port 250 °C, flow rate 40 ml He/min.

Sidestream Smoke

The smoke that emerges from a burning cigarette between puffs (static burn) is defined as sidestream smoke. For the analysis, 10 weight-selected cigarettes were smoked in the sidestream chamber [36]. Only 1 cigarette was smoked at a time by a single-port, piston-type machine. The sidestream smoke was led into 2 gas wash bottles at an airflow rate of 25 ml/sec. The cigarette holder of the sidestream chamber was slightly modified in contrast to the one used in an earlier study [1]. The work-up of the trapped smoke was identical with that of the mainstream smoke described above.

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Results and Discussion

In order to determine the volatile nitrosamines in Swiss and German cigarettes, the method published by one of the authors *(K.D.B.)* was applied and the values shown in tables II and III were obtained by the other authors (*W.F.* and *F.M.*). The values for the mainstream smoke are quite comparable to those found in an earlier study [1]. For practical reasons, the traces of DEN are not tabulated. In general, all cigarettes with cellulose acetate filter tips have much lower concentrations of these volatile nitrosamines in the mainstream smoke, confirming the effect of selective filtration [1].

The nitrosamine values obtained for the sidestream smoke from German and Swiss cigarettes exceed those of the mainstream smoke significantly although they appear somewhat lower than those reported earlier [1]. This can be explained by several reasons. The values in tables II and III are not corrected for losses during the analysis. When separate recovery experiments using DMN-^{14}C were performed, the recovery varied from 78 to 80%; in the case of NPY-^{14}C, we recovered 85–90% because of the lesser volatility of NPY. The cigarette holder of the sidestream apparatus has been modified with a rubber holder which may also, in part, explain the different results. In order to

Table II. Volatile nitrosamines in commercial Swiss cigarettes (ng/cigarette)[1]

Brand	Length, mm	Mainstream smoke			Sidestream smoke		
		DMN	MEN	NPY	DMN	MEN	NPY
A, F	79	17	1.8	8.2	195	8.1	28
B, F	79	17	n.d.	13	361	12	101
C, F	79	9.5	n.d.	20	317	19	143
D, NF	72	27	1.2	13	359	15	90
E, F	79	1.5	n.d.	3.5	223	19	49
F, F	79	9.3	n.d.	6.3	276	9	114
G, F	79	0.5	n.d.	1.8	415	27	114
H, F	79	n.d.	n.d.	1.5	233	n.d.	79
I, F	84	2.8	n.d.	9.7	223	7	70
J, F	84	5.3	n.d.	16	274	15	97
K, F	85	0.1	n.d.	3	218	5	87
L, F	90	1.5	n.d.	19	143	7	49

F = Filter; NF = nonfilter; n.d. = not determined.

[1] Isolated values, recovery of DMN-^{14}C = 78–80%, NPY-^{14}C = 85–90%.

Table III. Volatile nitrosamines in commercial German cigarettes (ng/cigarette)[1]

Brand	Length, mm	Mainstream smoke			Sidestream smoke		
		DMN	MEN	NPY	DMN	MEN	NPY
A, F	84	4.7	n.d.	3.9	398	24	150
B, F	84	5.9	0.1	8.3	297	6.1	65
C, F	85	0.4	n.d.	8.1	175	15	66
D, NF	85	20	2.5	29	401	19	107
E, NF	85	1.6	n.d.	2.4	155	3.1	86
F, NF	85	2.7	n.d.	4.9	270	6.3	84
G, F	84	0.2	n.d.	4.8	229	9.1	72
H, F	84	n.d.	n.d.	8.1	210	6.0	84
I, F	85	1.8	n.d.	7.4	184	6.7	50
J, NF	85	6.7	n.d.	15	294	7.7	93

F = Filter; NF = nonfilter; n.d. = not determined.

[1] Isolated values, recovery of DMN-^{14}C = 78–80%, NPY-^{14}C = 85–90%.

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explore the experimental differences, we smoked cigarettes A, D and E from an earlier study [1] (American brands) and obtained between 26 and 64% lower values for DMN and NPY than obtained in New York in 1977 indicating not only different experimental variations but also possible changes in the tobacco composition of these brands since the analyses were performed nearly 2 years apart.

Many investigators have analyzed tobacco smoke constituents in indoor environments and attempted to extrapolate the effects on the nonsmoker [38–42]. In a recent study, the concentration of DMN in various indoor environments was described [38]. The air in these rooms was sampled with a portable vacuum pump housed in an attaché case.

In order to study the relationship of smoke concentration and DMN content in a significantly larger enclosure than the sidestream chamber, we used an experimental chamber of 20.87 m^3 size. To exclude any interference from noncontrollable conditions, the walls were covered with porcelain tiles, the window was covered with dark paper and the room was well sealed. An automatic 30-port smoking machine was used to generate the smoke from experimental cigarettes, and between 450 and 680 liters of air were sampled. Figure 1 illustrates the relationship of smoke concentration and DMN content in the chamber; an excellent correlation was observed (r^2=0.996). This also demonstrates that the chamber was well sealed and that no condensation on the walls or chemical changes occurred. When two other experimental cigarettes were smoked, similar correlations were observed (table IV). When calculating the DMN concentration per cigarette smoked, we obtained between 68 and 87% of the values obtained when smoking these cigarettes in the experimental sidestream apparatus. For our purpose, the chamber served merely as an intermediate tool.

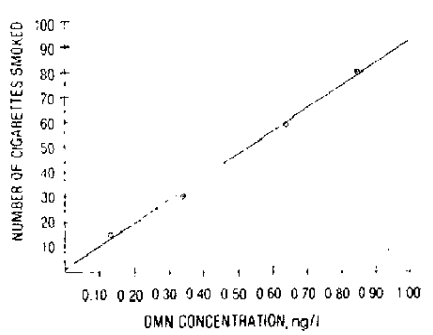

Fig. 1. DMN concentration as a function of cigarettes smoked in experimental chamber.

Table IV. DMN in experimental chamber (20.87 m^3) using experimental cigarettes

Brand	Cigarettes smoked	DMN[1] ng/l	DMN ng/cig
Monitor I	15	0.13	177
F (80 mm)	30	0.34	236
	59	0.64	228
	80	0.85	221
			$\bar{X}$ = 216 = 68%[2]
E-76	15	0.15	204
F (85 mm)	30	0.34	239
	43	0.45	218
	51	0.57	234
	76	0.90	246
			$\bar{X}$ = 228 = 87%[2]
Monitor II	15	0.11	152
F (80 mm)	30	0.32	219
	45	0.54	252
	60	0.69	238
	79	1.14	302
			$\bar{X}$ = 232 = 84%[2]

[1] Volume sampled: 450–680 liters.
[2] Percent of the value found when small sidestream chamber is used.

One should be aware, however, that the conditions used in the experimental chamber are not realistic in terms of human exposure to tobacco smoke since five cigarettes smoked in a room of 30 m^3 size already cause a degree of irritation [43] which prevents anyone's remaining in such an environment.

Finally, the discussion remains of how valid the method is which we applied here. Although there may be shortcomings with this method, to our knowledge no other such reliable and rapid analytical method exists. However, we are currently studying the mechanism of artifactual formation and the use of other inhibiting agents [44–47] as well as construction designs of other sidestream chambers.

Both the laboratory sidestream apparatus and the sealed experimental chamber are artificial model devices set up for analytical purposes. Their relevance to actual realistic conditions was not the objective of this study. Our aim was to provide controlled conditions for the generation and sampling of cigarette smoke with the objective to study nitrosamine formation and to apply the methods to product research with the goal of eliminating the nitrosamines.

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Klaus D. Brunnemann, Philip Morris Europe, Research Division, CH-2003 Neuchâtel (Switzerland)

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